REMARKS

Status of the Claims

Claims 1-3 and 5-31 were rejected in the Final Office Action of August 8, 2003 and the rejections were maintained in the Advisory Action mailed October 29, 2003. Claim 3 was cancelled in response to the Final Office Action. Upon entry of this response claims 1-2 and 5-31 will be pending.

No new matter has been added.

Rejections under 35 U.S.C. § 103

Claims 1-2 and 5-8 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Malik *et al.*(*Blood* 86:2993-3005, 1996, hereinafter "Malik") in view of Dropulic *et al.* (U.S. Patent No. 5,887,767, hereinafter "Dropulic"), Kataoka *et al.* (*Journal of Biological Chemistry* 272:18209-18215, 1997, hereinafter "Kataoka") and Horvai *et al.* (*PNAS* 92:5591-5393, 1995, hereinafter "Horvai"). Applicants respectfully disagree.

In the Advisory Action the Office states:

> It is noted that the amendment of claims by inserting the limitation "wherein the DNA molecule is a plasmid" does not obviate the rejection because Malik *et al.* does teach plasmids that comprise macrophage cell specific expression of the sequence of interest in a macrophage cell line.

(Advisory Action, page 2). Applicants respectfully disagree with the Office's reading of the Malik reference. Malik discusses the expression of a sequence in a CD34+ cell using a retroviral vector. Malik ***fails to*** teach or even suggest the direct administration of plasmids for macrophage cell specific expression. Malik constructs the viral expression system which uses a plasmid that contains the CD11b promoter as a starting material to produce, in a non-macrophage packaging cell line, a retroviral genome, which is RNA, not DNA, that is packaged within a retroviral particle produced by the non-macrophage packaging cell line PA317 (see, Malik, Materials and Methods, p. 2994). PA317 is ***not*** a macrophage cell or one that is derived from a macrophage cell, but instead was derived from NIH-3T3 cells (a fibroblast cell line). The PA317 cells then produce a virus (*i.e.* an

RNA virus that serves as a viral vector) that is able to infect another cell. The sequence that is expressed in the macrophage cell is delivered to the cell as an RNA molecule packaged in a retroviral particle, not by a plasmid DNA molecule. Malik teaches the delivery of the RNA molecule to the cells using the retroviral particles in the supernatant of the PA317 packaging cells to infect macrophage cells ands deliver the nucleic acid sequence for expression and production of the protein (see, Malik). The plasmid that is described in Malik is ***not*** transfected, injected, or delivered to a macrophage cell but rather used to produce a viral particle that is used to infect a macrophage cell and deliver to the macrophage cell an RNA molecule within the viral particle. None of the secondary references teach or suggest modifying the teachings of Malik to produce the present invention. None of the references either alone or in combination discuss or suggest administering a DNA molecule or plasmid to express a sequence in a macrophage cell. Therefore, the cited references do not support the Office's allegation that the present invention is prima facie obvious.

For the references to render the present invention obvious the combination of the references must yield the current invention as described in the pending claims. If one of ordinary skill in the art were to combine the cited references, the result would be administering to an individual at a site on the individual's body the viral supernatant of a packaging cell line, not a plasmid as described in the pending claims.

One of skill in the art would not have been motivated to modify the references to yield the present invention, because to do so would thoroughly destroy the intent of the Malik reference. By teaching the use of retrovirus vectors to deliver genetic material and express proteins in macrophage cells, the Malik reference teaches away from the present invention. One of ordinary skill in the art reading Malik reference would draw from its teachings that non-macrophage retroviral packaging cell lines should be transfected with plasmid DNA to produce viral particles containing RNA that can be used to infect macrophage cells and produce proteins encoded by the RNA of the viral particles. When combining references, the Office cannot pick and choose parts of a reference to be used in a combination and ignore those parts of the reference that teach away from the

invention. When viewed as a whole the references teaches away from combining it with the secondary references and clearly teaches away from the claimed invention. The Malik reference studied the retroviral mediated gene expression in human myelomonocytic cells. To suddenly interpret the Malik reference as administering a plasmid would be completely opposite of what is being studied in Malik. Therefore, one of skill in the art would not have been motivated to modify or combine the cited references to produce Applicants' invention.

Accordingly, the Office has failed to support its allegation that the present invention is *prima facie* obvious because the cited references either alone or in combination do not yield the current invention when. Additionally, there is no motivation to modify the reference for the reasons discussed above. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 1-2 and 5-8 stand rejected under 35 U.S.C. § 112, first paragraph, because allegedly the specification, while being enabling for an in vitro method of delivering a protein to a macrophage cell or a cell of macrophage derived lineage, does not reasonably provide enablement for an in vivo method. Applicants respectfully disagree.

Claims 9-31 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not describe in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The crux of the rejection as discussed in the Final Office Action, the Advisory Action, and the telephonic interview (October 27, 2003) is that there is no evidence in the specification or in the art of the record that it would not be routine to be able to identify a lymph node and be able to deliver to a lymph node a DNA molecule. Applicants respectfully disagree.

In support of Applicants assertion that it would be routine to identify a lymph node and the drainage pattern to a specific lymph node(s) Applicants provide herewith an unexecuted copy of a declaration of Dr. David B. Weiner pursuant to 37 CFR § 1.132. Applicants will promptly forward to the PTO an executed copy of the Declaration and Exhibit 1 upon their receipt by Applicants' undersigned representative. The declaration contains Exhibits 2-4 that indicate the level of skill and knowledge of those in the art at the time the above-identified application was filed. The exhibits demonstrate that drainage patterns associated with parts of the lymphatic system were reasonably understood and predictable at the time the invention was made. The exhibits also demonstrate that one of skill in the art could routinely determine the drainage pattern(s) of the lymphatic system and correlate a site of injection to a particular lymph node(s) using routine methodology without undue experimentation. The declaration clearly states that "at the time the invention was made one of skill in the art could identify the site of administration required to deliver a DNA molecule to a specific lymph node based upon the lymphatic drainage system that was either known or that was determined using techniques that would not require undue experimentation" (Declaration, page 2, 6).

Accordingly, the delivery of a DNA molecule based on the present specification and the knowledge of one of skill in the art would require nothing more than routine experimentation and would not be undue.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112 be withdrawn.

Conclusion

Applicants believe the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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Attachments:
Unexecuted Declaration under 1.132
Exhibit 2: Oncolog, taken from www3.mdanswerson.org/~oncolog/map.html
Exhibit 3: www.nucmednet.com/lymph.htm, entitled "Procedure of the Month November 1997
Exhibit 4: Eddy *et al. World J. Surg.* (2001) 25:794-797